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Review

Environmental health impacts of microplastics exposure on structural organization levels in the human body

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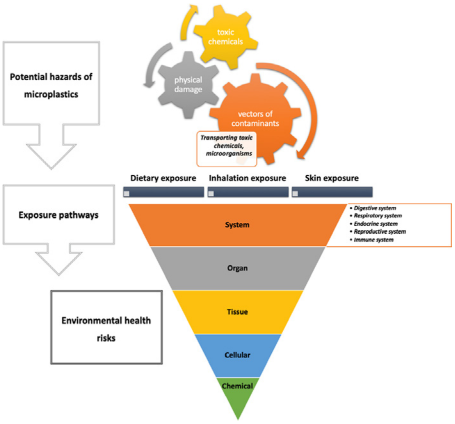
HIGHLIGHTS

- Evidence about potential human health risks of microplastics exposure
- Interactions of microplastics with environmental health on different levels
- Address the complex environmental health issues of microplastics pollution
- Five urgent perspectives and implications for future research on microplastics

GRAPHICAL ABSTRACT



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ABSTRACT

The ubiquitous prevalence of microplastics pollution has raised concerns about microplastics' potential risks and impacts on the global environment. However, the potential human health risks and impacts of microplastics remain largely unexplored. By providing an overview regarding the interaction of microplastics and human health, this review extends current knowledge on the potential impacts of microplastics pollution on humans from an environmental health perspective. The paper firstly presents the characteristics of microplastics as well as the status of global microplastics pollution. As for human health, the potential hazards of microplastics are reflected by toxic chemical components, vectors of contaminants, and physical damage. Extensive microplastic pollution on ecosystems due to human activities leads to inevitable human exposure, which may occur by dietary, inhalation and/or skin contact. Accordingly, microplastics exposure is closely associated with human health. This study explores the potential interactions of microplastics with the biological organization at various levels, including chemical, cellular, tissue, organ, and system levels. The review concludes by highlighting five urgent perspectives and implications for future research on microplastics: 1) Developing a standard terminology and research methods; 2) Reinforcing microplastics pollution governance; 3) Exploring innovative strategies and technologies; 4) Engaging the public and change behaviour; and 5) Adopting a transdisciplinary approach.

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1. Introduction

Plastic production has increased dramatically since the introduction of plastics in the 1950s. The term “microplastics” was introduced for “microscopic plastic fragments and fibers” in 2004 (Thompson et al., 2004). Over the last decade, microplastics pollution has been identified as a growing global threat that might affect ecosystems, biodiversity, and human health (Barboza et al., 2018a). The persistent contaminants of microplastics in ecosystems have also been recognized as an emerging global issue (Warning and Assessment, 2011). The contemporary period has been defined as “a new historical epoch, the Plasticene”, due to the extensive deposits of microplastics (Reed, 2015). The ubiquitous plastic pollution is widely acknowledged as a global threat to the natural environment and human and animal health, which is partly associated with bioactive plastics (Zarus et al., 2021). Furthermore, during the coronavirus (COVID-19) crisis, the world faces additional problems related to the widespread use of face masks and surgical gloves, which have contributed to the extensive amount of medical waste generated (Aragaw, 2020; Fadare and Okoffo, 2020; Saadat et al., 2020). The improper disposal and mismanagement of the environmental waste could induce microplastics pollution (Du et al., 2022). The correlation of face masks usage and the inhalation of microplastics is also worthy of attention (Torres-Agullo et al., 2021).

1.1. Characteristics of microplastics

The definition of microplastics has still not reached a broad consensus. Microplastics can be characterized in diverse ways. However, the defining properties need to include a consideration of size and origin and their physical and chemical nature (Frias and Nash, 2019). The characteristics of microplastics are commonly discussed in terms of their size, composition, source, and type.

Microplastics refer to small particles of plastics but the upper and lower size limits for microplastic particles are not well-defined. Early studies described microplastics as “plastic particles with a diameter < 5 mm” (Arthur et al., 2009). In general, larger pieces are called mesoplastics (Andrady, 2011) and macroplastics (Ryan et al., 2009), and smaller particles as nanoplastics (Costa et al., 2016) and sub-nanoplastics (Waring et al., 2018).

Plastics may comprise various materials and include complex additives. The precise chemical composition will have a significant impact on the state of microplastic pollution. For example, denser particles like polyamide (PA) and polyvinyl chloride (PVC) tend to settle to the ocean bottom. In contrast, the lighter forms such as high-density polyethylene (PE), polypropylene (PP), solid and foamed polystyrene (PS) typically float on the ocean surface (Embrandiri et al., 2020). Although no standard definition for microplastics' composition has been established, some scholars have suggested specifying the material composition of plastic debris, for example, in terms of “consisting of synthetic or heavily modified natural polymers”, or “whether they are solid and insoluble in water at 20°C" (Hartmann et al., 2019). In addition, some materials are poorly defined and need to be specified further. For example, there is no consensus on whether paints, tyre-wear particles, or polymer gels should be regarded as plastics (Rist, 2019). In particular, even for microplastics with the same origins and compositions, the physical properties may differ due to a particle's size, shape, and age (Lambert et al., 2017).

Furthermore, microplastics can be classified as primary microplastics and secondary microplastics according to the plastics' origin (Hartmann et al., 2019). Primary microplastics may be manufactured for indirect use as precursors or direct use like microbeads in personal care and cosmetic products (PCCPs) (Bergmann et al., 2015). These microbeads have been adopted as scrubbing agents in facial cleansers, shower gel, toothpaste, etc. So et al. (2018) reported that >60% of surface coastal water samples contain plastic microbeads. Secondary microplastics can be made up from large plastic debris' fragmentation and weathering (Marsden et al., 2019). Microplastics can be formed through a combination of photooxidation by ultraviolet (UV) and mechanical or biological degradation, eventually becoming smaller fragments (Galloway et al., 2017).

Another classification of microplastics is based on their types and shapes, including pellets, fragments, fibres, film, rope and filaments, microbeads, sponges or foam, and rubber (Frias et al., 2018). Some shapes of microplastics tend to be dominant in certain circumstances due to natural sorting processes. For instance, fibrous microplastics are the dominant type among fibres, fragments, and granules (Jin et al., 2018b). One study on American adults and children showed that the vast majority of microplastic particles consumed are fibres that could originate from water, alcohol, air, seafood, sugar, and honey (Cox et al., 2019). Due to the various criteria adopted to identify microplastics, applying a unified definition to existing studies is not practical. To avoid confusion, the term "microplastics" are defined as plastic particles with a diameter < 5 mm, including those in the nanometre size range, in this review.

1.2. Effects of microplastics pollution on ecosystems due to human activity

Human activities play a vital role in influencing ecosystems with the ubiquitous footprint of microplastics influencing being detected in almost all environmental matrices (Mu et al., 2019). Microplastics pollution is not only found in regions with intense human activity but also sparsely populated areas like the Arctic Polar Region (Halsband and Herzke, 2019) and the Tibetan Plateau, the "Third Pole" of the world (Zhang et al., 2021). These observations demonstrate how pervasive modern pollution is and how it has become an impending threat to environmental sustainability.

Microplastics have invaded our everyday lives because of human activities, urbanization, industrial activities, etc. It has been postulated that "stealth microplastics" will induce the disruption of many ecosystems (Embrandiri et al., 2020). Sources of microplastics include tyre and road wear particles, laundry, household dust, and PCCPs (Napper and Thompson, 2016; Siegfried et al., 2017). Other examples include discharges from sewage treatment facilities (Lo et al., 2018) and the increasing production and use of synthetic fabrics globally, which after processing through domestic washing machines, has become a critical origin of microplastics into aquatic ecosystems (Yang et al., 2019a). Also, microplastics pollution can generate from ocean-based sources, such as the abrasion of ropes, and enter the marine environment directly (Napper et al., 2022).

In summary, as the extensive persistence and accumulation of microplastics in ecosystems across the world are an evidently environmental health issue. However, our knowledge of the potential risks of microplastics pollution on human health is relatively limited. Consequently, the interaction of microplastic environmental impacts and the rising prevalence of related human diseases is still controversial. This article firstly examines the potential hazards of microplastics. Moreover, the possible pathways of microplastics entering the human body and the potential health risks will be reviewed emphasizing different chemical, cellular, tissue, organ, and system levels. The research aims to better understand the complex environmental health issues of microplastic pollution to formulate directions for future microplastics research.

2. Potential hazards of microplastics to human health

The physicochemical property of microplastics pay an important role in influencing human health. For instance, smaller size as well as microfibers are relatively more dangerous microplastics types to human (Ebrahimi et al., 2022; Liu et al., 2019a). There are three main microplastic health hazards: (1) Leaching of toxic chemical components, including constituents and additives (inorganic and organic); (2) As chemical or biological vectors with microplastics adsorbing harmful extraneous substances; (3) Direct physical damage from plastic debris, such as an obstruction in various organs due to ingested particles.

2.1. Toxic chemical components

Plastics have a significant global production: from 1 to 37 million tonnes annually (Lithner et al., 2011). Thus, the continuous release of microplastics into ecosystems has been referred to as a "chemical time bomb" (Zhao et al., 2019). Release of the plastic polymers may pose both environmental and health hazards (Campanale et al., 2020; Oliveira et al., 2019). The physical and chemical toxicities of microplastics pollution are potentially dependent on microplastics' dose, size, polymer type, shape, surface chemistry, and hydrophobicity, which can influence microplastic bioavailability (Botterell et al., 2019; Smith et al., 2018). Various additional chemicals can be added in the process of the plastic manufacturing (Hahladakis et al., 2018). The additives can also be toxic to humans, even at extremely low concentrations (Azoulay et al., 2019). Among the chemical additives, the biological effects of phthalates and bisphenol A (BPA) are of particular concern. Both chemicals have been shown to affect the hormone system's functioning and are known as "endocrine disrupters". Such chemicals can mimic natural hormones in the body, induce energy and fat metabolism changes, and cause health problems such as diabetes and obesity (Teuten et al., 2009).

The medical evidence of links to human diseases by persistent organic pollutants (POPs) is robust, including cancers and tumours, neurological disorders and deficits, reproductive disorders, and other diseases in humans and wildlife (Azoulay et al., 2019). Diethylhexyl phthalate (DEHP), a phthalate often used to make PVC softer, may constitute up to 50% of the plastics' weight and is reported to be carcinogenic (Cole et al., 2011). The etiological correlation between exposure to toxicants (e.g., BPA and DEHP) and the development of autism disorders have also been reported in children (Ye et al., 2017). Furthermore, flame retardants are widely used in plastics (Pivnenko et al., 2017; Yang et al., 2019b). One study suggests that co-exposure to microplastics and flame retardants may induce enhanced oxidative stress-mediated neurotoxicity in mice (Deng et al., 2018).

2.2. Vectors of contaminants

Another potential threat of microplastics to human health is that they can serve as vectors for dispersing toxic chemicals and biological agents, which can occur as absorption, adsorption, or both (Rist, 2019). Also, microplastics' surface area to volume ratio and hydrophobicity are relatively high, and they may change the co-contaminant bioavailability (Sleight et al., 2017). Microplastic can transport associated organic contaminants, heavy metals, harmful microbes and pathogens into the environment, where they may have chemical, microbiological, and environmental effects (Boelee et al., 2019).

In addition, microplastics can accumulate inorganic and organic pollutants from the ambient environment and subsequently liberate them into other ecosystems, resulting in significant hazards to humans (Xu et al., 2019; Amelia et al., 2021). Plastics can adsorb chemicals, heavy metals or other toxic contaminants from water with subsequent release in different environments (Azoulay et al., 2019). For instance, the adsorption of heavy metals to microplastics has been identified on beaches (Li et al., 2020b). Organisms may consume chemicals and heavy metals adsorbed on microplastics, then transported to the human digestive system through food chain (Yang et al., 2015; Zhang et al., 2019). For instance, microplastics have been shown to act as a chromium vector in a whole digestive system in-vitro model with high non-carcinogenic risks to humans (Liao and Yang, 2020).

Microplastics can also act as vehicles or vectors for diverse microscopic organisms. People are exposed to plastics via dermal contact or ingestion of microbially contaminated microplastics (Boelee et al., 2019). Microplastics may convey antibiotic resistance genes among various environments and animals (Liu et al., 2021). With regard to the outbreak of COVID-19, it has been reported that the coronavirus can stay infectious on plastic materials for nine days (Kampf et al., 2020). The microbial hazards of plastics are thus potentially important in transferring epidemic diseases. Biofilm formation on microplastics may affect microbial transmission through microbial–microplastic–toxic chemical interactions (Verla et al., 2019). Nutrient concentrations, salinity, temperature, UV radiation, and oxygen content may influence biofilm formation (Oberbeckmann et al., 2018). In drinking water, biofilms on microplastics can be formed when microorganisms grow on water pipes which may flake away due to aging (Marsden et al., 2019).

2.3. Physical damage

Microplastics' direct physical effects on animals have been widely reported, especially for marine organisms. Damage can be induced by abrasions of the digestive system, decreased growth rates, and so on (Wright et al., 2013). There are many microplastic risks in humans, including the possibility of crossing biological boundaries once inside the body. It has, for instance, been reported that PE particles in artificial joint replacements have been disseminated to the patients' abdominal lymphatic system and liver (Hicks et al., 1996; Urban et al., 2000).

3. Exposure pathways of microplastics to the human body

Contemporary studies have documented the potential chemical, microbial, and particle hazards of microplastics, ubiquitous in most ecosystems, leading to inevitable human exposure (Kontrick, 2018). Current knowledge about the scale of microplastic exposure levels in humans is poor, and there is a need for a thorough understanding of exposure concentrations, physicochemical properties, contaminants of concern, involved tissues, and personal susceptibility of microplastics (Joon, 2019; Koelmans et al., 2017; Prata et al., 2019; Revel et al., 2018). Chronic microplastics' exposure may be even having significant concern given their potential accumulative effect in a dose dependent manner (Wright and Kelly, 2017a).

There are three main pathways of human microplastics exposure (Fig. 1): (1) dietary exposure; (2) inhalation exposure; (3) skin contact (Prata et al., 2019).

3.1. Dietary exposure pathway

It is becoming increasingly evident that microplastics are able to be ingested by different species of wildlife, which may enter the food chain through our diet (Karbalaei et al., 2018; Lehner et al., 2019). Drinking water, food, and plastic food packaging are also significant sources of

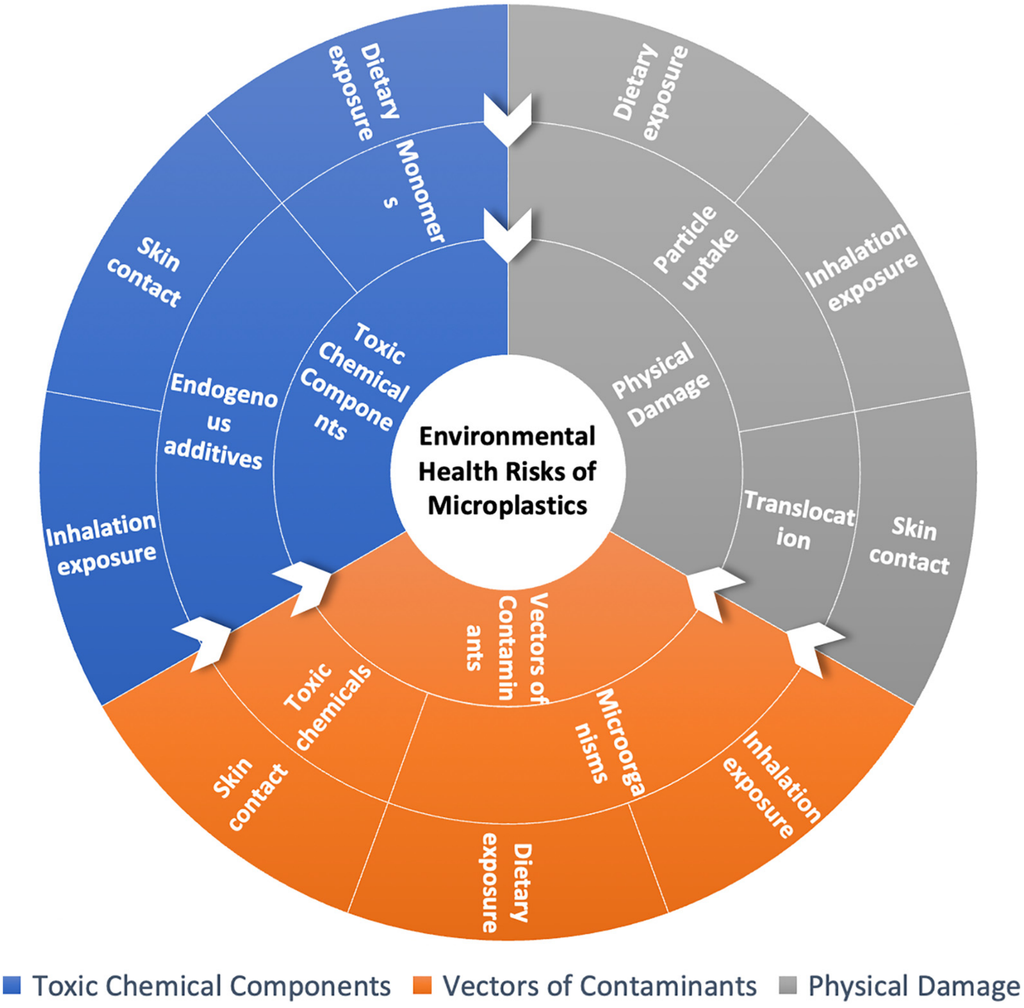

Fig. 1. Simplified scheme illustrating potential human health risks from microplastics pollution. The environmental health risks of microplastics are reflected in the toxic chemicals, vectors of contaminants and physical damage, which might bring adverse consequences to human health by dietary, inhalation and skin exposure pathways.

microplastics and associated toxic contaminants (Qu et al., 2015). Consequently, microplastic contamination in the diet is becoming a significant issue for food safety.

3.1.1. Microplastics in seafood

Given the prevalence of microplastics in aquatic environments worldwide (Sundbæk et al., 2018; Wang et al., 2020), microplastics contamination have been detected in several kinds of seafood, which may pose a significant risk to consumers. They are often eaten whole, including the gastrointestinal tracts and gills, which are known sites of microplastics contamination (Smith et al., 2018). Moreover, Pfaller et al. (2020) demonstrated that the odour from plastic debris would elicit foraging behaviour in sea turtles, suggesting the attractiveness of microplastics to marine animals originate from not only the way it looks but also the way it smells.

Consuming microplastic-contaminated bivalves is one of the leading dietary risks of microplastics exposure to human health, as microplastics are widely present in cultured mussels and oysters (Van Cauwenberghe and Janssen, 2014; Zhu et al., 2019). Li et al. (2018) found that mussels collected from coastal waters and supermarkets contained microplastics and predicted that consumers ingest 70 microplastic items in 100 g of mussels. The translocation of microplastics has been demonstrated across the gastrointestinal lymphatics to the circulatory system (Hussain et al., 2001). Microplastics were also detected in sardines and sprats cans (Karami et al., 2018) and the organs (e.g., stomach contents and liver) of fish *Squalius cephalus* (Collard et al., 2018). It has also been reported that consuming Mud carp (*Cirrhinus molitorella*) and Bighead carp (*Hypophthalmichthys nobilis*) have the potential risk of accumulating phthalate esters during gastrointestinal (GI) digestion (Cheng et al., 2013). Regarding the abundance of ingested microplastics, no significant difference was found among several species and sources of fish. In contrast, spatial variation did exist. Fish close to urban areas are more readily to ingest microplastics (Chan et al., 2019).

3.1.2. Table salt

Microplastics have been detected in table salt derived from seas, lakes, wells, and rock salt in various countries (Gündoğdu, 2018; Yang et al., 2015). As commercial salt is a prime edible commodity, microplastic contamination would pose a particular threat to public health (Selvam et al., 2020). Lee et al. (2019) found that 94% of commercial table salt contained microplastics, with polyethylene terephthalate (PET), PP, and PE the most common polymer types. Consequently, humans may be ingesting several hundred microplastic items from salt consumption annually. Salt is used daily in human diets and thus constitutes a long-term exposure route (Peixoto et al., 2019).

3.1.3. Drinking water

Several studies reported microplastics in tap water (Kosuth et al., 2018), bottled water (Mason et al., 2018; Oßmann et al., 2018), and groundwater sources (Mintenig et al., 2019). For instance, Schymanski et al. (2018) examined water from various containers, and found that beverage cartons, plastic and glass bottles all contained microplastics. Surface run-off and wastewater effluent are important inputs of microplastics into freshwater (Marsden et al., 2019). Treatment plants and conventional treatment processes can prevent microplastics from entering drinking water (Novotna et al., 2019). However, some contamination may be caused by plastic equipment's abrasion during water purification and distribution processes (Mintenig et al., 2019). Whether some microplastics contamination is due to laboratory procedures remains controversial (Lachenmeier et al., 2015).

3.1.4. Other foods

Plants are exposed to microplastics directly when organic fertilizer, sludge, plastic mulch, wastewater, and plastic litter are applied to soils and through surface runoff and microplastics aerosols. It has been estimated that people might consume 80 g of microplastics through edible plants daily (Ebere et al., 2019). Sun et al. (2020) demonstrated that plastics accumulate in *Arabidopsis thaliana* depending on their surface charge. For instance, positively charged nanoplastics are more likely to accumulate at low levels in the root tips. In contrast, negatively charged microplastics are often observed in the apoplast as well as the xylem. The presence of microplastics was investigated in vegetables such as carrots, lettuce, broccoli, potato, and fruits such as apples and pears (Conti et al., 2020).

3.1.5. Food packaging

Food processing and packaging can also contaminate foods with microplastics (Silvestre et al., 2011). A take-away cup has a lining of PE, which can only be treated by a particular recycling facility (Embrandiri et al., 2020). Microplastic contamination of packaged meat has been detected. Microplastics can be derived from food trays, as they are typically made from extruded PS (Kedzierski et al., 2020). Surprisingly, Hernandez et al. (2019) showed that certain teabags could release billions of nylon and PET particles per cup. For plastic bottled mineral water, microplastic contamination was strongly correlated with water pH, the density, and the plastic thickness of the bottle (Zuccarello et al., 2019). One study demonstrated the release of microplastics from mechanical stress, repeatedly opening and closing the bottles with plastic caps (Winkler et al., 2019).

3.2. Inhalation exposure pathway

Airborne microplastics are an underestimated risk, with particles potentially reaching deep inside human lungs as they can bypass respiratory tract defense. Microplastics are one of the constituents of particulate matter that is increasingly being recognized as a grave public health hazard (Abbasi et al., 2019; Raj et al., 2018). Most alarmingly, ubiquitous indoor dust also contains microplastics (Enyoh et al., 2019).

Microplastics have been found in house dust, where it constitutes a non-negligible fraction of indoor airborne particulates (Vianello et al., 2019). Microfibers are the dominant form in the atmosphere. They can reach the respiratory system of humans and pose health risks, particularly to industrial workers (Chen et al., 2019; Kaya et al., 2018). One study on workers exposed to microplastics has also documented the development of colorectal cancer. Several animal studies also indicate that microplastic fibres may degrade in the lungs and exert harmful effects (Zarus et al., 2021).

Tyres, road-wear particles (Kole et al., 2017), aerosol formation from sea salt, the wind-driven release of wastewater sludge (Lehner et al., 2019), degradation of construction materials, clothes drying, apparel, and synthetic textiles (Henry et al., 2019) are all potentially significant sources of airborne microplastics (Lehner et al., 2019). Liu et al. (2019b) reported that around 120.72 kg of suspended atmospheric microplastics is annually transported through the atmosphere in Shanghai. Approximately 21 microplastic particles can be inhaled daily by an adult. Furthermore, airborne microplastics may also carry pathogens to the human lung through biofilms, resulting in infections (Prata, 2018).

3.3. Skin contact

Humans may also be exposed to microplastics through skin contact following atmospheric fallout of synthetic fibres, and microbeads in cosmetic products (Leslie, 2014). Hair follicles, sweat glands, or injured skin are all possible entry routes (Schneider et al., 2009). Moreover, it has been reported that particles below 100 nm may traverse the dermal barrier and penetrate through human skin (Revel et al., 2018). Microbeads used in PCCPs and their fragmentation may lead to hazardous nanoplastics (Hernandez et al., 2017). Moreover, Kuo et al. (2009) proved that chemical enhancers, such as oleic acid and ethanol, could enhance the transdermal delivery of nanoparticles. Specifically, dermal contact with microplastics may also be associated with plastic glitters, which are made from PET or PVC, and appear in cosmetic, craft activities and textile products (Yurtsever, 2019).

4. Potential human health risks from microplastics pollution

Human health risks from microplastics pollution are associated with the microplastic-specific exposure and the human organs involved, as well as

Table 1
Overview of the potential interactions of microplastics with environmental health on different levels of biological organization.

Level of biological organization	Biological effects	Species	Reference
Chemical level			
	IL-6 gene↑, IL-8 gene↑	human gastric adenocarcinoma cells	(Forte et al., 2016)
	IL-8 gene↑	A549 epithelial cells	(Brown et al., 2001)
	SOD3↑, Casp3↑, Tp53↑, CXCR5↑	fish, the sheepshead minnow (*Cyprinodon variegatus*).	(Choi et al., 2018)
	Oxidative stress responses↑, anti-oxidant↑, glutathione-related enzymes↑	marine mussels *Mytilus* spp.	(Paul-Pont et al., 2016)
	transcription of genes involved in energy metabolism and development	pacific oyster *Crassostrea gigas*	(Sussarellu et al., 2016)
	DNA damage↑	*Daphnia magna* and shrimp *Neocaridina davidi*	(Berber, 2019)
	Genotoxic↑		
	ROS↑		
Cellular level			
	Endocytosis	A549 cells;	(Salvati et al., 2011)
	intracellular endocytotic pathway by accumulating in lysosomes	endothelial cell line EAhy926;	(Fröhlich et al., 2012)
		primary human renal epithelial cells	(Monti et al., 2015)
	neurotoxic effects and oxidative stress ↑	epithelial human cells	(Schirinzi et al., 2017)
	intracellular ROS ↑	human colonic epithelial cells CCD841CoN and small intestinal epithelial cells HIEC-6	(Zhang et al., 2022)
	oxidative stress ↑		
	mitochondrial depolarization ↑		
	neurotoxic effects and oxidative stress ↑	marine planktonic crustaceans	(Gambardella et al., 2017)
	immunomodulation, apoptosis ↑	marine bivalve *Mytilus*	(Canesi et al., 2015)
	MAPKs signaling related inflammation and apoptosis↑	monogonont rotifer (*Brachionus koreanus*)	(Jeong et al., 2016)
Tissue level			
	Energy deficiency: ATP↓	mice	(Deng et al., 2017)
	Lipid metabolism disturbance: total T-CHO↓, TG↓		
	Oxidative stress: GSH-Px↑, SOD↑, CAT↓		
	Neurotoxic responses: AChE activity ↑		
	histopathological changes: tissue alterations, occurrence of neutrophils	adult zebrafish	(Limonta et al., 2019)
	structural changes and necrosis	Mediterranean mussels (*M. galloprovincialis*)	(Bråte et al., 2018)
	strong inflammatory responses and tissue alterations	the blue mussel *Mytilus edulis*	(Von Moos et al., 2012)
Organ level			
	Histopathological change: inhaled fibres in histopathology slides	human lung tissues	(Pauly et al., 1998)
	Translocation across membranes ↑	rats	(Kreyling et al., 2009)
	Bioaccumulation of nanoplastics and microplastics	mice	(Meng et al., 2022)
	Kidney damage and nephrotoxicity		
	Penetrate the BBB	fish, Crucian carp, *Carassius carassius*)	(Mattsson et al., 2017)
	Oxidative stress and damage in liver ↑	crab *Dicentrarchus labrax juveniles*	(Barboza et al., 2018b)
System level			
Digestive system	Nine plastic types of microplastics were found	human stool	(Schwabl et al., 2019)
	Microplastics were detected in eleven colectomy samples	human colectomy specimens	(Ibrahim et al., 2021)
	iron absorption↑	chicken	(Mahler et al., 2012)
	remodeling of the intestinal villi		
	Gut microbiota dysbiosis↑, hepatic lipid metabolism disorder↑	mice	(Lu et al., 2018)
	the secretion of mucin in gut↓		
	gst-4 expression↑	zebrafish *Danio rerio*, nematode *Caenorhabditis elegans*	(Lei et al., 2018)
	intestinal Ca2 + ↓		
	Microbiota dysbiosis and inflammation in the gut	zebrafish	(Jin et al., 2018a)
	Microflora dysbiosis:	crab Juvenile *Eriocheir sinensis*	(Liu et al., 2019c)
	fusobacteria↑, proteobacteria↑		
	firmicutes↓, bacteroidetes↓		
Respiratory system	Oxidative stress: ROS↑	normal human lung epithelial BEAS-2B cells	(Dong et al., 2020)
	α1-antitrypsin↓, transepithelial electrical resistance by depleting zonula occludens proteins↓		
	CXCL5↑, G-CSF↑	cystic fibrosis mouse model	(Geiser et al., 2014)
	15-HETE↓		
	TGF-β↑, TNF-α↑	Sprague-Dawley rats	(Lim et al., 2021)
Endocrine system	liver enzymes GGT↑	human urine	(Lang et al., 2008)
	Body mass index↑, waist circumference↑	human urine	(Do Minh et al., 2017)
Reproductive System	Microplastics were detected	human placenta	(Ragusa et al., 2021)
	Ovarian response↓, number of fertilized oocytes↓, blastocyst formation↓	Human	(Vandenberg et al., 2009)
	Birth weight in offspring↓	human	(Miao et al., 2011)
	Oocyte number↓, diameter↓,sperm velocity↓	oysters	(Sussarellu et al., 2016)
	Feeding capacity↓, reproductive output↓	pelagic copepod *Calanus helgolandicus*.	(Cole et al., 2015)
	Impaired development and reproduction↑	pacific oysters *Crassostrea gigas*	(Tallec et al., 2018)
	Fertilization success↓		
Immune system	ROS generation↑, endoplasmic reticulum stress↑	human lung epithelial (BEAS-2B) cells	(Chiu et al., 2015)
	Complement system genes (cfhl3, cfhl4, cfb and c9) ↑	zebrafish larvae	(Veneman et al., 2017)
	PRRs and AMPs family↑	edible mussel *Mytilus galloprovincialis*.	(Détrée and Gallardo-Escárate, 2018)
	Caspase↑, MyD88↑	crab Juvenile *Eriocheir sinensis*	(Liu et al., 2019c)
	haemocyanin (Hc)↓, alkaline phosphatase (AKP)↓, phenoloxidase (PO)↓, lysozyme (LSZ)↓, acid phosphatase (ACP)↓		

the length of exposure, thus it is critical to identify the possible influences across all biological levels (Rahman et al., 2021). Hence, to gain a broad picture, the impacts associated with microplastics exposure are explored according to the levels of the human body's structural organization from chemical to cellular, tissue, organ, and system levels of biological organization (Table 1). As for this topic, studies on humans directly are limited at this stage. Therefore, we include related research on other organisms to generate a broader picture from an environmental health perspective. The information we present follows humans, other mammals, fish, and other organisms like bivalves.

The implications of microplastic exposure to various organisms on a system-level basis are reviewed; to provide comprehensive information the interaction of microplastics with the human body at different levels are examined along with the potential biological consequences.

4.1. Chemical level

Microplastics exposure may alter gene expression within several species at the subcellular level, especially the transcription of genes involved in cellular stress response, immune functions (Liu et al., 2019d), energy metabolism, and development (Sussarellu et al., 2016). The increase of reactive oxygen species (ROS) may lead to eventual DNA damage (Berber, 2019). An in-vitro study showed that nanoplastics could significantly upregulate interleukin genes in human gastric adenocarcinoma cells, and these genes represent cytokines in the pathology of gastric diseases by affecting cell viability, inflammatory as well as cell morphology (Forte et al., 2016). Similarly, increased expression of interleukin 8 gene and pro-inflammatory responses of human A549 lung cells were found upon microplastics exposure (Brown et al., 2001).

PS microbead ingestion by mussels leads to a series of oxidative stress responses, including increased haemocyte mortality and imbalanced cellular oxidative impacts, specifically upregulated ROS production in haemocytes, anti-oxidant effects, etc. (Paul-Pont et al., 2016). Jeong et al. (2016) used in vitro tests to identify the defense mechanisms activated by microplastics exposure. They revealed that the related enzymes as well as the status of mitogen-activated protein kinases (MAPKs) were significantly activated in a size dependent manner. In addition, it has been reported that microplastics accumulated in fish digestive systems regulated ROS-related genes and enzymatic activities. For instance, the transcriptional levels of the oxidative stress gene superoxide dismutase 3 (SOD 3), apoptosis related gene caspase 3 (Casp3) and Tp53 and immune response-related gene chemokine (C-X-C motif) receptor 5 (CXCR5) were all up-regulated by microplastics exposure (Choi et al., 2018).

4.2. Cellular level

The cellular uptake and translocation of particles are significantly influenced by their interactions with surrounding proteins, phospholipids, carbohydrates and specific cell types, and the size, surface chemistry, concentration, and charge of the particles (Lehner et al., 2019; Mahmoudi et al., 2011). In addition, some extremely small particles are able to cross membranes, such as the blood-brain barrier (BBB) and placenta (Vethaak and Leslie, 2016). These processes have several mechanism pathways, including endocytosis, passive diffusion, adhesive interaction, protein-mediated uptake, etc. (Krug and Wick, 2011; Monti et al., 2015).

Studies of the translocation of PS nanoparticles in human cell lines have demonstrated that these particles can be internalized, and induce oxidative stress as well as inflammatory responses (Lehner et al., 2019). Salvati et al. (2011) presented an uptake study in A549 cells and demonstrated that the endocytosis of PS nanoparticles follows the intracellular endocytotic pathway by accumulating in lysosomes. The accumulation of nanoparticles in the lysosome is essentially irreversible (Fröhlich et al., 2012). Furthermore, the potential toxic effects of microplastics have also been shown in human intestinal normal cell lines (Zhang et al., 2022).

Induced neurotoxic effects and oxidative stress have been found after microplastics treatment in marine planktonic crustaceans (Gambardella et al., 2017). In addition, by evaluating ROS effect and cell viability, oxidative stress has been found in human cerebral cells and epithelial cells (Schirinzi et al., 2017). Furthermore, significant antioxidant responses to microplastic exposure have also been observed in the blue mussel. These included SOD activities, catalase (CAT), glutathione peroxidases, and total glutathione levels observed in gills and digestive glands (Magara et al., 2018). Microplastics' combined effects have been found at the subcellular and cellular levels in organisms. For instance, the activated antioxidant-related enzymes, p-JNK, and p-p38, and MAPKs signaling pathways are closely associated with cellular inflammation and apoptosis (Jeong et al., 2016).

4.3. Tissue level

In general, interactions between tissue and organs occur with protein-coated nanoparticles but not bare ones, such as the formation of protein corona around nanoparticle surfaces, and its physicochemical changes may alter the nanoparticle's biological responses, characteristics and properties (Treuel et al., 2014).

At the tissue level, the accumulation of microplastics has been demonstrated with the kinetics and distribution pattern significantly dependent on size. Additionally, the accumulation of microplastics may induce various effects on biomarkers, and metabolomics. The disruptions to energy and lipid metabolism are represented by increased lactate dehydrogenase activity and decreased adenosine triphosphate (ATP), total cholesterol (T-CHO), and triglycerides (TG). The induced oxidative stress can be observed from upregulated glutathione peroxidase (GSH-Px) and SOD and downregulated CAT. In particular, blood biomarkers of neurotoxicity acetylcholinesterase (AChE) were actively increased, suggesting that microplastics exposure induced widespread health risks (Deng et al., 2017). Structural changes and necrosis in tissues were observed in Mediterranean mussels induced by the uptake of PE particles isolated from toothpaste (Bråte et al., 2018). Blue mussels also showed significant inflammatory responses and tissue alterations after experimental microplastics exposure (Von Moos et al., 2012).

4.4. Organ level

Human organs are at risk of chronic microplastics exposure (Bergmann et al., 2015; Lehner et al., 2019). The exposure may occur in the GI tracts and lungs, except for endocytosis (Rist et al., 2018). Still, there is no consensus as to the size of the particle where this is possible, with estimates ranging from <1.5 μm (EFSA, 2016) to 5 or 20 μm (Deng and Zhang, 2019). Also, it is established that microplastics can subsequently spread to other tissues and organs. Meng et al. (2022) demonstrated that the bioaccumulation of nanoparticles and microplastics in the kidney of mice via oral exposure, which can cause renal impairment by participating in systemic circulation.

The translocation of nanoparticles across membranes into secondary target organs has been observed in rats (Kreyling et al., 2009). One laboratory research project showed that plastic nanoparticles can even penetrate the BBB in fish, and induce behavioural disorders (Mattsson et al., 2017). Moreover, the oxidative stress and damage caused by microplastics exposure have also been observed in the liver of fish *Dicentrarchus labrax* juveniles (Barboza et al., 2018b).

4.5. System level

The human body is made of eleven crucial organ systems. A system consists of related organs with a common function, and these systems work together to maintain a functioning human body. One organ can be part of more than one system, such as the pancreas, which belongs to the digestive system and the hormone-producing endocrine system (Tortora and Derrickson, 2018). One study has demonstrated that the toxicity between microplastics and nanoplastics is not the same in different systems. For instance, nanoplastics may cause more serious toxicity damage in the reproductive system than microplastics (Yin et al., 2021). Thus, interactions between microplastics and the body vary widely. The potential impacts of microplastics in the digestive, respiratory, endocrine, reproductive and immune systems are highlighted below.

4.5.1. Digestive system

Human health risks of microplastics could come from the chemical contaminants and the biomagnification of microplastics (Carbery et al., 2018). The large surface areas and charge of lumen can also induce complex adsorptive reactions, which may influence the gut immune system and complex adsorptive reactions, which may influence the gut immune system and cause intestinal irritation and inflammation like macrophages activation and cytokine production (Bouwmeester et al., 2015). Although the formation of a plastic bezoar (Yaka et al., 2015) in the digestive system is rare, the existence of microplastics has indeed been demonstrated in human faeces. Nine microplastic compositions have been detected in human stools, with PP accounting for the majority (62.8%). This suggested inadvertent microplastics ingestion from various sources (Schwabl et al., 2019). Furthermore, microplastics were detected in human colectomy specimens, indicating that microplastics are ubiquitously present in the human digestive tract (Ibrahim et al., 2021). PS nanoparticles in chicken-induced remodeling of the intestinal villi and upregulated iron absorption, suggest that microplastics exposure may affect the gut epithelium' barrier properties (Mahler et al., 2012).

Several studies have demonstrated that gut microbiota is closely correlated with host health, and there is an interaction between the mucosal immune system, epithelial barrier, and microbiome. Consequently, gut microbiota can be an essential aspect of microplastics issues (Jin et al., 2019; Li et al., 2020a; Lu et al., 2019). For instance, PS microplastics induce the imbalance of gut microbiota and intestine inflammation in zebrafish (Jin et al., 2018a). Also, PS particles exposure has been shown to cause disorder of hepatic lipid metabolism by reducing the secretion of mucin in the gut of mice (Lu et al., 2018). In addition, microplastics may cause direct and indirect intestinal enterocyte damage in zebrafish *Danio rerio* and nematode *Caenorhabditis elegans* by reducing intestinal Ca^{2+} and increasing *gst-4* expression (Lei et al., 2018). Microplastic exposure has also altered the diversity and composition of the intestinal microbiota profile of crab juvenile *Eriocheir sinensis* (Liu et al., 2019c).

4.5.2. Respiratory system

Most inhaled microplastics can be cleared in human lungs by mechanical methods, phagocytosis, and lymphatic transport. However, some may deposit in the lung triggering subsequent inflammatory responses like oxidative stress, translocation, and gene mutation, leading to acute and chronic respiratory diseases (Prata, 2018). Especially for individuals with respiratory disease or people under chronic occupational exposure to microplastics, such as people working in the textile industry and plants that make PE and PP, who have been shown to develop airway and interstitial lung diseases (Wright and Kelly, 2017b).

One recent research exercise verified the association between microplastics and pulmonary toxicity in human lung cells, and a high-dose PS microplastics exposure may increase the risk of chronic obstructive pulmonary disease (Dong et al., 2020). Moreover, one example of increased susceptibility of lungs to hazards from inhaled nanoparticles was reported in a murine cystic fibrosis model (Geiser et al., 2014). The potential mechanism involved augmented CXCL5 levels, upregulated G-CSF, and decreased 15-HETE levels, which enhanced exposure-related polymorphonuclear cell (PMN) accumulation on the airway surface. One recent study shows that subacute exposure to polystyrene micro(nano)plastics (PSMPs) poses potential health risks on Sprague-Dawley rats. After 14-day of inhalation exposure, protein expressions of TGF-β and TNF-α, which are the fibrosis and inflammatory-related factors, are promoted. This suggested that the inhalation of PSMPs contributed to the manifest molecular effect, and prolonged exposure may eventually lead to impacts at even higher levels (Lim et al., 2021).

4.5.3. Endocrine system

Several compounds in microplastics are regarded as endocrine disrupting chemicals (EDCs), and these chemicals may alter the endocrine system's function. Although most microplastics exposure can be characterized as low, increasing evidence suggests that the effect of EDCs chronic exposure in humans should not be dismissed as harmless (Vandenberg et al., 2017). One prominent example of EDC is BPA which can cause adverse effects because of its significant estrogenic activity (Hengstler et al., 2011). High BPA concentrations in adults' urine are also related to increased Gamma-glutamyl transferase (GGT) and avoidable morbidity from cardiovascular disease as well as Type 2 diabetes (Lang et al., 2008). Also, one report from a Canadian health measures survey showed that high levels of BPA were linked to higher odds of obesity and elevated waist circumference (Do Minh et al., 2017).

4.5.4. Reproductive system

One recent study demonstrated that microplastics were detected in placenta, which were collected from six patients with uneventful pregnancies (Ragusa et al., 2021). Elevated exposure of EDCs to childbearing-age women and children is of specific concern, which may increase the adverse outcome due to increased adverse effects such as breast cancer risk and endometriosis (Vandenberg et al., 2009). It was found that high urinary BPA concentrations were related to decreased ovarian response and blastocyst formation among women undergoing in vitro fertilization, indicating that BPA may alter early reproductive health outcomes (Ehrlich et al., 2012). Furthermore, research has identified a dependent relationship between the levels of BPA exposure in pregnancy and the magnitude of decreased birth weight of offspring (Miao et al., 2011). Several studies have explored the reproductive output of marine organisms due to microplastics exposure. In one study on pacific oysters, nanoplastics significantly decreased fertilization rates, and impaired gametes and embryos (Tallec et al., 2018). Similarly, copepods under microplastics exposure demonstrated a reduced feeding capacity and reproductive output, leading to reductions in ingested carbon biomass (Cole et al., 2015).

4.5.5. Immune system

Microplastics may induce toxicity and inflammation in the human body. Suppose the innate immune system cannot remove the particles at the beginning. In that case, the exposure and accumulation of microplastics may induce chronic inflammation, homeostasis alteration, and increased risk of immune disorders, neurodegenerative diseases, and cancers (Détrée and Gallardo-Escárate, 2018. Prata et al., 2019). The modulation of gene expression and proteins related to the immune reaction have been extensively investigated. For instance, one *in vitro* study on human lung cells revealed that PS nanoparticles can activate the innate immune system through increasing autophagic flux (Chiu et al., 2015). Moreover, another study reported that PS microplastics could activate complement system genes in zebrafish larvae, indicating that microparticles were integrated with the processes of immunological recognition (Veneman et al., 2017). In addition, it was reported that microplastics exposure affects the immunity genes expression of the pattern recognition receptors (PRRs) and the antimicrobial peptides (AMPs) family, which have an essential role in the immune system (Détrée and Gallardo-Escárate, 2018). Due to the stress induced by microplastics, it downregulated activities of various immune-related factors. Meanwhile, the haemocyte expressions of caspase and MyD88 were high regulated, indicating that microplastics provoke different immune inhibition levels in innate immunity (Liu et al., 2019c).

5. Future perspectives

There are several compelling knowledge gaps regarding sources, composition, and pathways of microplastics and human health risk assessments that must be filled urgently. The available literature suggests several key priorities that need to be examined in greater detail to improve our understanding of the risks from microplastics pollution and on how management actions may be developed to deal with these issues: These priority areas include: 1) Developing a standard terminology and research methods; 2) Reinforcing microplastics pollution governance; 3) Exploring innovative strategies and technologies; 4) Engaging the public and change behaviour, and 5) Adopting a transdisciplinary approach.

5.1. Developing a standard terminology and research methods

The ambiguous terminology of microplastics may compromise related research development. For instance, the lack of consensus on a specific definition of plastic debris may generate incomparable data (Hartmann et al., 2019). Another reason for the difficulties in comparing existing studies is the lack of standard methods for sampling, quantifying, and analyzing microplastics. There is an urgent need to improve microplastics sampling and analysis by developing quality assured procedures to facilitate the communication of results (Oliveira and Almeida, 2019). Although some efforts at defining standard methodological criteria for microplastics research have been made, including evaluation of existing methods (Thiele et al., 2019), exploration of the procedures (Su et al., 2018), protocols (Hermsen et al., 2018) and techniques (Covernton et al., 2019), more consensus on these standards among scientists is needed globally. Therefore, the first step to address the knowledge gap of microplastics studies is to determine standardized terminology and develop unified standard methods for microplastics related research.

5.2. Reinforcing microplastics pollution governance

Microplastics pollution is closely intertwined with global processes, as an emerging anthropocene risk, this issue deserves careful management and prevention (Villarrubia-Gómez et al., 2018). Plastic waste management and governance are critical for eliminating the environmental health impacts of this form of pollution.

Various governmental and non-governmental organizations have attempted to set guidelines for controlling microplastics. For instance, microbeads have been gradually banned in several countries worldwide (Guerranti et al., 2019). *A scheme on the regulation of disposable plastic tableware* is under discussion and public consultation in Hong Kong (The Government of the Hong Kong Special Administrative Region, 2021). China has also announced a ban on PCCPs containing plastic microbeads during late 2020, and will be prohibiting the sale of chemical products containing plastic microbeads by the end of 2022 (National Development and Reform Commission [2020] No. 80).

Despite recent improvements in global governance, the dispersal, durability, and mobility of microplastics, accelerated production, globalized consumption, diversified pollution sources, and obscured responsibility in international trade, all make governance extremely hard. There is a demand for more effective domestic industry regulation and an international plastics agreement (Dauvergne, 2018). In addition, for the adoption of plastic policies, environmental arguments instead of health concerns about microplastics pollution have been adopted to corroborate their support for the policies (Mederake and Knoblauch, 2019), suggesting the lack of awareness of the environmental health risk of plastic pollution. Thus, one of the greatest challenges that should be addressed is the timely control of plastic pollution. Evidence-based policies should control the plastics pollution issue. Several policy making strategies have been suggested, emphasizing individual and corporate social responsibility, forbidding the use of particular types of plastics and promoting alternatives, improving the facilities of wastewater treatment, etc. (Calero et al., 2021).

5.3. Exploring innovative strategies and technologies

The rapid accumulation of plastic waste driving global demand for innovation and investment towards sustainable manufacturing practices. Biotechnology-based strategies are regarded as one of the most promising approaches to solving environmental microplastics pollution. Bioplastics could be bio-based, biodegradable, or both, integrated with a sustainable and circular economic model (Paço et al., 2019). Ideally, biodegradable plastics should be non-bioaccumulative, non-toxic without harmful by-products (Brandon and Criddle, 2019). They can also act as long-term carbon sinks if well integrated into large-scale bioplastic-based infrastructure (Karan et al., 2019). However, critical voices note that biodegradable plastics are merely a distraction from real solutions towards the plastic pollution crisis, suggesting that priority should be given to preventing the production of plastics in the first place, followed by reuse and recycling (Zumstein et al., 2019).

Meanwhile, there is a need to develop innovative technologies for detection and identification of microplastics studies, such as improving the approach of sampling, sample pre-treatment, classification, and analysis (Becucci et al., 2022; Tirkey and Upadhyay, 2021; Ye et al., 2021). For instance, micro-FTIR is one of the typical apparatuses for quantification and identification of microplastics simultaneously; the procedure-related novel methods are developing and updating for generating more accurate data (Corami et al., 2021). Apart from analyzing microplastics in the environment, the detection of microplastics in the human body is also vital for conducting research on identifying human health risks. For example, Huang et al. (2022) studied the quantity of microplastics in human sputum by infrared absorption spectroscopy, which provided evidence of potential respiratory diseases caused by microplastics pollution.

5.4. Engaging the public and changing behaviour

The challenges of balancing the convenience of plastics with the possibility of causing microplastics pollution are of societal importance. Without immediate strong preventive actions, the environmental health impacts of microplastics would lead to severe problems locally and globally. Thus, there is an urgent need to raise public awareness of consumption choices and to engage the public in minimizing plastic waste. We should emphasise a bottom-up strategy and follow the “avoid the avoidable” principle (Embrandiri et al., 2020).

One survey on public attitudes towards plastic reports that 80% of the respondents are concerned about plastics as an environmental issue, yet few transform the aspiration into real action (Dilkes-Hoffman et al., 2019). However, to achieve a sustainable environment, each person must accept responsibility for environmental preservation and protection. We should not only engage in talk but also translate it into action. Human beings are the cause and solution of the problem. Thus, the importance of including the human dimension in microplastics-related research is critical. To address the environmental health impacts of microplastics, we need to work together across disciplines and sectors by integrating behavioural science and natural science and building on humans' strengths to facilitate behavioural change (Pahl et al., 2017).

Citizen science involves public engagement in research, in which volunteers can contribute to the monitoring of plastic pollution (Forrest et al., 2019). As an inclusive and participatory approach, citizen science can catalyze enabling more public engagement and action in the field (Allen et al., 2019; Zettler et al., 2017). Furthermore, public engagement also includes various educational activities in schools or a variety of societal organizations. For instance, experiential marine debris education has been shown to successfully improve students' knowledge of microplastics and empower their behaviour (Owens, 2018). Therefore, education is a key tool to develop ecological awareness and to bring good practices to the broader public and their attitudes. Furthermore, Garcia-Vazquez et al. (2021) have pointed out that psychosocial drivers for reducing are worth studying in order to reduce microplastics pollution.

5.5. Adopting a transdisciplinary approach

Microplastics pollution has evolved from being a problem to a cross-cutting crisis and environmental health issue worldwide, impacting both natural and human environments. They also pose interdependent risks between the environment and the health of animals and humans (Prata et al., 2021). There is a need for holistic approaches to address the widespread and complex nature of the issue by developing overarching local to global governance (Vince and Stoett, 2018). The nature of microplastics pollution require collective action to address the various social, health, and environmental challenges (Sly et al., 2016; Yang and Lo, 2021). Thus, researchers from ecological, medical and social sectors should collaborate to resolve the many issues. A transdisciplinary approach is needed to address the issues' complexity and to better integrate academic studies into decision-making (Vethaak and Legler, 2021).

6. Conclusions

Microplastics research is an evolving field that is increasingly exploring potential impacts on human health with many possible controversial relationships. Existing studies indicate the potential chemical, microbial, and particle hazards of microplastics that may interact with the human body through a wide range of exposure pathways, including ingestion, inhalation or skin contact. More studies on microplastics pollution are required to evaluate the interactions between microplastics and human health. Nevertheless, there is sufficient scientific evidence to support urgent preventive measures by the scientific, industrial, and policy development communities to prevent ongoing microplastics pollution (Gallo et al., 2018).

From an environmental health perspective, this review presents the potential hazards of microplastics to human health as reflected in the relevant toxic chemicals and vectors of contaminants that cause biological, chemical or physical damage. The study also notes the role of extensive microplastics pollution of natural ecosystems caused by human activities, which, in turn, leads to inevitable human exposure and human health risks. However, a complete understanding of potential problems can be gained by examining microplastics and their impacts at contrasting levels.

In conclusion, we should not see microplastics as micro and thus a minor problem, as it matters for an eco-friendly earth and for better human health. Research requires a focus on the specific environmental health impacts, and we need to immediately solve this problem at international, national, and local levels.

CRediT authorship contribution statement

Xi Yang: Conceptualization, Writing – original draft, Writing – review & editing. **Yu Bon Man:** Writing – review & editing. **Ming Hung Wong:** Writing – review & editing. **Richard Bernhart Owen:** Writing – review & editing. **Ka Lai Chow:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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